REMARKS

Claims 1 and 11 have been amended to specify that the purified, collagen-based matrix structure has an endotoxin level of less than 5 endotoxin units per gram. Support for these claim amendments is found on page 14, line 19 and in original claim 3 of the specification as filed. Support is also found in the priority document, U.S. Application Serial No. 60/024,542, on page 7, lines 16-17. Claims 4-6 and 9-10 have been amended to incorporate the language of original claim 1. Claim 9 has also been amended to indicate that the submucosa tissue is treated with an oxidizing agent "prior to delamination." Support is found, for example, in original claim 16 and on page 8, lines 16-19 of the specification as filed. Claims 2-3, 7-8, 12-15, and 21-34 have been canceled without prejudice.

(1) Claim Objections

The Examiner has objected to claims 22, 23, 25, 26, 28, 29, and 31-34 regarding claim informalities. Claims 22, 23, 25, 26, 28, 29, and 31-34 have been canceled without prejudice. Thus, the Examiner's objection is moot.

(2) Claim Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 21-34 under 35 U.S.C. § 112, first paragraph, asserting that the claims do not comply with the written description requirement. Claims 21-34 have been canceled without prejudice. Therefore, the Examiner's rejection for lack of an adequate written description is moot.

(3) Specification Objections

Similarly, the Examiner's objection to the specification regarding proper antecedent basis of the claim term "endogenous" has been mooted with the cancelation of claims 21-34.

(4) Claim Rejections under 35 U.S.C. § 102 over Abraham et al.

(a) Rejection of claims 1-6, 11 and 14

The Examiner has rejected claims 1-6, 11 and 14 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,993,844 to Abraham et al. (the '844 patent). The Examiner indicates that the '844 patent anticipates claims 1-6, 11, and 14 because the '844 patent describes graft constructs that are endotoxin-free and, further according to the Examiner, a graft construct that is "endotoxin-free" is within the ranges claimed in the present application. Furthermore, the Examiner asserts that the effective filing date of the present claims is August 22, 1997 because, according to the Examiner, support for the range of "an endotoxin level of less than 12 endotoxin units per gram" is not present in the provisional applications from which the instant application claims priority. Claims 2-3 and 14 have been canceled without prejudice. Regarding pending claims 1, 4-6, and 11, Applicants respectfully traverse the Examiner's rejection.

First, amended claims 1 and 11 are not anticipated by the '844 patent because the claimed subject matter has an effective filing date before the effective filing date of the '844 patent. In relevant part, prior art references properly cited under 35 U.S.C. § 102(e) include "a patent granted on an application for patent by another filed in the United States *before* the invention by the applicant for patent." 35 U.S.C. § 102(e) (emphasis added). The application filing date of the '844 patent is May 8, 1997. Thus, if the claimed subject matter of Applicants' application has an effective filing date before May 8, 1997, a rejection of the present claims under 35 U.S.C. § 102(e) in view of the '844 patent is improper.

Applicants' claims as amended have an effective filing date before the effective filing date of the '844 patent (i.e., May 8, 1997). Independent claims 1 and 11 have been amended to specify that the purified, collagen-based matrix structure has an endotoxin level of less than 5 endotoxin units per gram. This amendment is supported by the disclosure of U.S. Provisional Application Serial No. 60/024,542 (the '542 application), a provisional application from which the present application claims priority. Specifically, the '542 application, filed on August 23, 1996, recites less than "5 EU/g" as a preferred endotoxin level on, for example, page 7, lines 16-17. Furthermore, the Examiner has conceded that "EU/g" is well-known in the art to mean "endotoxin units per gram" (see last paragraph on page 6 of the September 10, 2007 office action). Accordingly, the claimed subject matter of amended claims 1 and 11 has an effective filing date of August 23, 1996 (i.e., the filing date of the '542 priority application). Therefore, the Examiner's rejection of claims 1 and 11 is improper because the '844 patent, filed on May 8, 1997, is not an appropriate prior art reference under 35 U.S.C. § 102(e). Claims 1 and 11 are not anticipated by the '844 patent, and withdrawal of the rejection of claims 1 and 11 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

Second, claims 4-6 are not anticipated by the '844 patent because the prior art does not set forth each and every element of the claims as amended. Anticipation exists only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In the instant rejection, the '844 patent does not describe grafts comprising a purified, collagen-based matrix structure with a bioburden level defined by colony forming units per gram. The '844 patent describes a chemical cleaning method that renders biologic material "substantially acellular and substantially free of non-collagenous components." (see column 4, lines 49-53 of the '844 patent). The phrase "substantially free of non-collagenous components" is defined in the '844 patent as amounts of

glycoproteins, glycosaminoglycans, proteoglycans, lipids, non-collagenous proteins and nucleic acids, such as DNA and RNA, that "comprise less than 5% of the resultant tissue matrix." (see column 4, lines 61-66 of the '844 patent). However, the '844 patent does not quantify the purification of tissue in terms of colony forming units. In fact, the term "colony forming unit" is ***completely absent*** from the '844 patent.

In contrast, amended claims 4-6 of the present application describe graft prostheses with a bioburden level defined in terms of colony forming units. Accordingly, the '844 patent does not each and every element as set forth in the claims as amended. Withdrawal of the rejection to claims 4-6 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(b) Rejection of claims 7-10 and 16-31

The Examiner has rejected claims 7-10 and 16-31 under 35 U.S.C. § 102(e) as allegedly being anticipated by the '844 patent or, in the alternative, as being obvious under 35 U.S.C. § 103(a) over the '844 patent. Claims 7-8 and 21-31 have been canceled without prejudice. Regarding pending claims 9-10 and 16-20, Applicants respectfully traverse the Examiner's rejection.

First, anticipation exists only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claims 9-10 and 16-20 are not anticipated by the '844 patent because the prior art does not set forth each and every element of the Applicants' amended claims.

As amended, independent claims 9, 10, and 16 are directed to a graft prosthesis comprising a purified, collagen-based matrix structure wherein the submucosa tissue source is cleaned or treated to remove contaminants ***before*** the submucosa tissue source is delaminated. Importantly, the '844 patent does not describe cleaning of the submucosa tissue prior to

delamination. In contrast, the '844 patent requires delamination of submucosa tissue prior to any cleaning of the tissue (see Example 1, found at column 11, line 34 to column 12, line 24 of the '844 patent). Accordingly, the '844 patent does not each and every element as set forth in the claims as amended.

Second, the Examiner has concluded that claims 7-10, 16-20, and 23-31 are product-by-process claims. According to MPEP § 2113, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the ***manufacturing process steps would be expected to impart distinctive structural characteristics to the final product***." MPEP § 2113 (quoting *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (emphasis added).

Claims 7-8 and 21-31 have been canceled without prejudice. If pending claims 9-10 and 16-20, are product-by-process claims (as indicated by the Examiner), the process steps impart the requisite distinctive structural characteristics to the final product. Claims 9-10 and 16-20 are each directed to a purified collagen-based matrix structure. As stated previously, the process steps in the claims describe preparation of the matrix structure wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated. Importantly, these process steps impart distinctive characteristics to the final purified product. In Examples 4 and 5 of the specification as filed, a purified product prepared according to the method described in claims 9-10 and 16-20 (i.e., wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated) was shown to have lower endotoxin levels compared to a product prepared according to methods where submucosa tissue was cleaned ***after*** the tissue was delaminated (see page 22, line 22 to page 23, line 17 of the specification as filed). Therefore, the process steps described in claims 9-10 and 16-20 impart distinctive structural characteristics (e.g, lower endotoxin levels) to the final product and

the matrix structure implied by the process steps of the claims should be considered when assessing the patentability of the claims over the prior art.

In contrast to the process steps of claims 9-10 and 16-20, the methods in the '844 patent describe a matrix of submucosa tissue that was cleaned ***after*** the tissue was delaminated. Thus, the matrix prepared according to the '844 patent has different structural characteristics than the matrix prepared according to Applicants' claims 9-10 and 16-20. Accordingly, if pending claims 9-10 and 16-20 are product-by-process claims as indicated by the Examiner, the claims are not anticipated by the '844 patent. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(5) Claim Rejections under 35 U.S.C. § 103 over Abraham et al.

(a) Rejection of claims 7-10 and 16-31

The Examiner has rejected claims 7-10 and 16-31, in the alternative, as being obvious under 35 U.S.C. § 103(a) over the '844 patent. Claims 7-8 and 21-31 have been canceled without prejudice. In regards to pending claims 9-10 and 16-20, Applicants respectfully traverse the Examiner's rejection.

First, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants' invention to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants' invention, as defined by claims 9-10 and 16-20.

The '844 patent does not teach or suggest cleaning of the submucosa tissue prior to delamination. Instead, the '844 patent requires delamination of submucosa tissue prior to any cleaning of the tissue (see Example 1, found at column 11, line 34 – column 12, line 24 of the '844 patent). As amended, claims 9-10 and 16-20 describe a submucosa tissue that is cleaned

prior to being delaminated. The '844 patent provides no suggestion of the claimed method. Accordingly, amended claims 9-10 and 16-20 are not obvious over the '844 patent. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness and the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 103 is improper. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 103(a) over the '844 patent is respectfully requested.

Second, the Examiner has concluded that claims 7-10, 16-20, and 23-31 are product-by-process claims. According to MPEP § 2113, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the ***manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.***" MPEP § 2113 (quoting *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (emphasis added).

Claims 7-8 and 21-31 have been canceled without prejudice. If pending claims 9-10 and 16-20, are product-by-process claims (as indicated by the Examiner), the process steps impart the requisite distinctive structural characteristics to the final product. Claims 9-10 and 16-20 are each directed to a purified collagen-based matrix structure. As stated previously, the process steps in the claims describe preparation of the matrix structure wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated. Importantly, these process steps impart distinctive characteristics to the final purified product. In Examples 4 and 5 of the specification as filed, a purified product prepared according to the method described in claims 9-10 and 16-20 (i.e., wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated) was shown to have lower endotoxin levels compared to a product prepared according to methods where submucosa tissue was cleaned ***after*** the tissue was delaminated (see page 22, line 22 to page 23, line 17 of the specification as filed). Therefore, the process steps described in claims 9-10 and 16-20

impart distinctive structural characteristics (e.g, lower endotoxin levels) to the final product and the matrix structure implied by the process steps of the claims should be considered when assessing the patentability of the claims over the prior art.

In contrast to the process steps of claims 9-10 and 16-20, the methods in the '844 patent describe a matrix of submucosa tissue that was cleaned ***after*** the tissue was delaminated. Thus, the matrix prepared according to the '844 patent has different structural characteristics than the matrix prepared according to Applicants' claims 9-10 and 16-20. Accordingly, if pending claims 9-10 and 16-20 are product-by-process claims as indicated by the Examiner, the claims are not anticipated by the '844 patent. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(b) Rejection of claims 12, 13, 32, and 33

The Examiner has rejected claims 12, 13, 32, and 33 under 35 U.S.C. § 103(a) as being obvious over the '844 patent alone. Claims 12, 13, 32, and 33 have been canceled without prejudice. Thus, the Examiner's rejection is moot.

(c) Rejection of claims 15 and 34

The Examiner has also rejected claims 15 and 34 under 35 U.S.C. § 103(a) as being obvious over the '844 patent in combination with Braun. Claims 15 and 34 have been canceled without prejudice. Thus, the Examiner's rejection is moot.

(6) Claim Rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 over Yannas et al.

The Examiner has rejected claims 1-3, 7-11, 13, and 14 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,060,081 to Yannas et al. (the '081 patent) or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over the '081 patent alone. The Examiner asserts that the '081 patent anticipates the claims of the instant application where purified collagen is used to make the graft because it is "indistinguishable from collagen of other

sources in that all the other source components have been removed." Furthermore, the Examiner contends that the purified structure described in the '081 patent is inherently free of endotoxins because all endotoxins have been removed. The Examiner also indicates that if a difference exists due to the source utilized to make the collagen, the difference is so slight that it would have been *prima facie* obvious to a person skilled in the art to arrive at the presently claimed invention from the teachings of the '081 patent. Applicants respectfully traverse the Examiner's rejection. Claims 2-3, 7-8, and 13-14 have been canceled without prejudice. Claims 1 and 9-11 are not anticipated by the '081 patent and, moreover, are not obvious over the '081 patent.

(a) Collagen Structure in the '081 Patent is not Inherently Free of Endotoxins

Moreover, the Examiner has not met his burden of proof to establish that the "purified" collagen structure in the '081 patent is inherently free of endotoxins. According to the Manual of Patent Examining Procedure, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." MPEP § 2112(IV) (quoting *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)) (emphasis original). In the present rejection, the Examiner simply states that the "purified" collagen structure in the '081 patent is inherently free of endotoxins.

After a thorough review of the methods described in the '081 patent, it is obvious that sterile techniques are not required during the preparation of the collagen structure. Examples 1-5, which describe the preparation of collagen dispersions and the crosslinking of collagen to form a composite structure, have no discussion of sterile techniques or purification procedures (see column 14, line 53 – column 16, line 44 of the '081 patent). Similarly, the '081 patent contains no discussion regarding the desire for low endotoxin levels in the collagen compositions. In fact, the terms "toxin" and "endotoxin" are ***completely absent*** from the text of the '081 patent, and no methods for removing endotoxins are described.

According to the Manual of Patent Examining Procedure, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112(IV) (emphasis original). In the present Office Action, the Examiner has simply stated that the collagen structure described in the '081 patent "is inherently free of endotoxins because all endotoxins have been removed." As stated previously, the term "endotoxin" is ***completely absent*** from the text of the '081 patent. Accordingly, the Examiner has not met his burden to prove that the "purified" collagen structure in the '081 patent is inherently free of endotoxins. Claims 1 and 9-11 of the present application are not anticipated by the '081 patent and are not obvious over the teachings of the '081 patent. Withdrawal of the rejection of claims 1 and 9-11 under 35 U.S.C. § 102(b) and under 35 U.S.C. § 103(a) in view of the '081 patent is respectfully requested.

CONCLUSION

The foregoing amendments and remarks are believed to fully respond to the Examiner's rejections. Applicants respectfully request issuance of an action indicating that the claims are allowable, and issuance of a declaration of interference.

Respectfully submitted,

Rebecca Ball

Rebecca Ball
Registration No. 46,535

RVB:EEW:glt
Indianapolis, Indiana 46204
INDS02 EEWILLIAMS 1093418v1